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CME Review

Penicillin and Cephalosporin allergy

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Target Audience: Physicians involved in providing patient care in the field of allergy/asthma/immunology
Learning Objectives:
At the conclusion of this activity, participants should be able to:

- Describe the component structures of penicillin and ampicillin accounting for allergy and the relationship of chemical structure of penicillins and cephalosporins in predicting cross reactivity
- Discuss the predictive value of penicillin, ampicillin and cephalosporin skin testing for identifying patients at risk for subsequent allergic reactions

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Introduction

In 2011, penicillins and cephalosporins were the top 2 antibacterial drugs sold in the United States, making up nearly 60% of all the antibacterial drug market.[1] As of April 2013, the Food and Drug

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Administration has approved more than 34 β-lactam compounds as active ingredients in drugs for human use.[2] In a recent report by the Allergy Vigilance Network of the European registry of recorded drug-induced severe anaphylaxis from 2002 to 2010, 42.6% of the cases were caused by penicillins, amoxicillin, and cephalosporins.[3,4]

Unfortunately, among physicians, a lack of knowledge still exists regarding the safe use of alternative β-lactams in penicillin allergic patients.[5] This review is intended to educate health care professionals regarding immunologic cross-reactivity of a patient with a penicillin allergy to certain cephalosporins and the structural explanation for this cross-reactivity.

There are a number of guidelines on the use of specific cephalosporin antibiotics for the treatment of patients with reported penicillin allergies provided that the penicillin reaction is not severe or of a type I allergic reaction (American Academy of Pediatrics 2001, American Academy of Pediatrics and American Academy of Family Physicians 2004, American Academy of Pediatrics acute otitis media guidelines 2013, American Academy of Pediatrics Sinusitis Guidelines 2013, and American Academy of Allergy, Asthma and Immunology 2010). This review provides evidence that supports and challenges those recommendations. Specifically, evidence that suggests the guidelines are too restrictive in providing cephalosporin options in penicillin allergic patients, including those with a history of severe or type I reactions to penicillin.[6,7]

Penicillins and Cephalosporins: Structure and Synthesis

Alexander Fleming is credited with the discovery of an antibacterial substance produced by a mold belonging to the genus *Penicillium* that he named penicillin. The structures of penicillin and some of its antibacterial derivatives are shown in Figure 1. The core structure of penicillin is the β-lactam ring with the variable side chain R attached to the amide bridge to the ring carbon 6 atom. Modifications at the R site have allowed for the development of penicillin-derivative antibiotics. β-Lactam antibiotics (BLAs) inhibit the bacterial transpeptidases (also called penicillin-binding proteins) that catalyze the peptidoglycan cross-linking reaction involved in bacterial cell wall biosynthesis. Shortly after the introduction of penicillin, bacterial resistance to penicillin emerged and there was a need for newer antibiotics. Similar to the discovery of penicillin, Giuseppe Brotzu in 1945 discovered cephalosporin C (also called penicillin N; C stands for chromatography) from a fungal microorganism, *Cephalosporium*, near a sewage outlet that demonstrated antibiotic activity against both gram-negative and gram-positive bacteria. Cephalosporin C had limited antibiotic activity, and it was not until 1964 that the first semisynthetic cephalosporin antibiotic compound, cephalothin, was marketed.

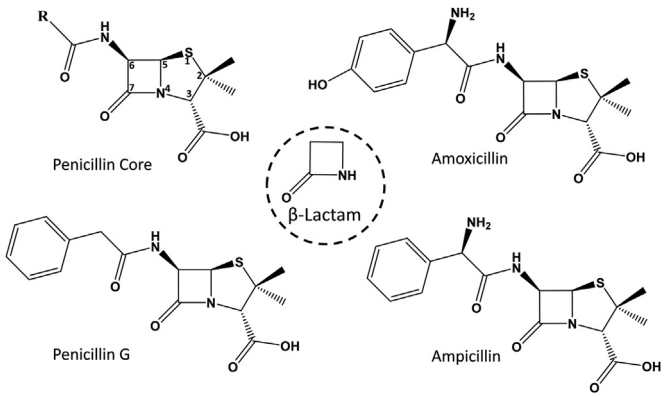


Figure 1. Basic structure of penicillins. Core structure of the β-lactam ring along with selected penicillin drugs showing the diversity of the R side chain.

The manufacture process of early cephalosporins involved starting with *Penicillium* mold production of penicillin and then chemical modification of the 5-membered thiazolidine ring attached to the β-lactam ring of penicillin to a 6-membered dihydrothiazine ring.[8] Then different side chains were added. Therefore, all of the early cephalosporins produced between the mid-1960s up until the mid-1980s had minor contamination by penicillin. Therein lies a possible explanation for the early results of studies by the allergy community showing significant cross-allergy between penicillins and cephalosporins.

First-generation cephalosporins were produced by chemically or enzymatically modifying the R1 site of the basic cephalosporin structure shown.[8,9] Subsequent generations of cephalosporins have been synthetically synthesized (Table 1). Second-generation and subsequent generations of the cephalosporins have modification at the R1 and R2 sites (Fig 2). Substitution at R sites (different side chains) provides variation in the spectrum of activity against different bacteria species and longer duration of action.

Classification of Antibiotic Drug Allergy

Classifications of β-lactam adverse reactions are based on the immunopathologic events of the patient responding to the allergen as originally proposed by Coombs and Gell.[10]

Type I (hypersensitivity) is an IgE-mediated reaction, with onset occurring minutes to hours after exposure, and is one of the most severe drug reactions. IgE receptors on tissue mast cells or circulating basophils bind to the allergen, releasing histamine and other mediators. These IgE-mediated reactions are clinically represented as urticarial rash, hypotension, rhinitis, bronchospasm, angioedema, and anaphylactic shock.[11,12] Guidelines make reference to type I allergy as noted above. The term is redundant because type I Coombs and Gell reactions are allergic reactions. Only the penicillin skin test and radioallergosorbent test is used for type I immune testing. (The radioallergosorbent test developed in 1974 has been replaced by more a sensitive fluorescent enzyme immunoassay (FEIA),[13] which is the recommended assay by the National Institute of Allergy and Infectious Disease.[14] In this article, we use the term *FEIA*.)

Type II (cytotoxic) immune reactions are IgG and IgM antibody–mediated cytotoxic reactions that involve activation of the complement system. These reactions are clinically represented as hemolytic anemia, thrombocytopenia, cytopenia, proteinuria, and hematuria that occur approximately 72 hours after drug exposure. Neither skin testing nor FEIA testing is of any value in detecting risk of type II reactions.

Type III (serum sickness) immune reactions are mediated by IgG and IgM, with the onset of symptoms occurring 10 to 21 days after exposure. The cause is circulating immune complexes that are deposited in blood vessels of the kidneys, joints, or skin, resulting in fever, vasculitis, interstitial nephritis, arthralgia, lymphadenopathy, splenomegaly, and/or erythema multiforme. Neither skin testing nor FEIA testing is of any value in detecting risk of type III reactions.

Type IV (delayed hypersensitivity) immune reactions are mediated by IgG and cellular responses. They occur approximately 72 hours after drug exposure. The most common type of type IV reactions is maculopapular exanthem. Neither skin testing nor FEIA testing is of any value in detecting risk of type IV reactions.

Many drug reactions do not fit into the Coombs and Gell classification and were proposed later as a “catch-bag” for reactions not meeting the criteria of types I to IV. These reactions have their onset typically after 72 hours and are nonspecific. They occur in 1% to 4% of patients receiving penicillin and cephalosporins and generally manifest as nonpruritic rashes. Neither skin testing nor FEIA testing is of any value in detecting risk of these reactions. However, oral challenge may reproduce the reaction, especially if the reaction is caused by an excipient ingredient in a liquid formulation of the antibiotic, such as a dye or flavoring.

Table 1
Generations of cephalosporins for human use[a]

First	Second	Third	Fourth	Fifth
Cefadroxil	Cefaclor	Cefcapene[b]	(Cefepime)	(Ceftaroline fosamil)
Cefazedone[b]	Cefamandole[c]	Cefdinir	Cefluprenam[b]	Ceftobiprole[b]
(Cefazolin)	Cefprozil	Cefditoren	(Cefozopran)[b]	
Cephalexin (Cefalexin)	Cefuroxime	Cefetamet[b]	Cefpirome[b]	
Cephalothin[c] (Cefalotin)	Cefuroxime axetil[d]	Cefixime	Cefclidine	
Cephradine[c] (Cefradine)	Cefonicid[c]	Cefmenoxime[c]	Cefquinome	
Cephaloridine[c] (Cefaloridine)	Cefmetazole[c,e]	Cefoperazone[c]	Cefoselis	
Cephapirin[c] (Cefapirin)	Cefotetan[e]	Cefotaxime	Flomoxef[f]	
Cefatrizine	Cefoxitin[e]	Cefpiramide[c]		
Cephaloglycin[c] (Cefaloglycin)	Loracarbef[c,g]	Cefpodoxime		
Cephacetrile (Cefacetrile)	(Cefminox)[b]	Cefsulodin[b]		
Ceftezole	(Cefbuperazone)[b]	Ceftibuten		
		Ceftizoxime[c]		
		Ceftriaxone		
		Moxalactam (Latamoxef)[c,f]		
		Ceftazidime		
		Cefodizime[b]		
		(Cefdaloxime)[b]		
		(Ceftiolene)[b]		
		(Cefteram)[b]		

[a]This table was generated in part from Chang C, Mahmood MM, Teuber SS, Gershwin ME. Overview of penicillin allergy. *Clin Rev Allergy Immunol* 2012;43:84-97. Names in parentheses are international nonproprietary names.
[b]Not approved in the United States.
[c]Discontinued in the United States (www.fda.gov/Drugs).
[d]Prodrug of cefuroxime for improved oral bioavailability.
[e]Cephamycins have a 7-α-methoxy group that gives resistance to β-lactamases and makes them different from other cephalosporins.
[f]Oxacephem, where the sulfur atom of the cephalosporin core is replaced with an oxygen atom.
[g]Loracarbef is a carbacephem, although typically grouped with cephalosporins.

Five Major Educational Messages

First, penicillin allergy does not occur in 10% of the population. When a patient gives a history of penicillin allergy, it is absolutely necessary to probe the authenticity of this information. The true incidence of penicillin allergy in patients who report that they are allergic is less than 10%.[15–20] Many patients consider a family history of penicillin allergy as applicable to themselves even if no reactions have occurred. Upset stomach, diarrhea, or a fleeting nonpruritic maculopapular rash may be considered by the patient to represent allergy.

In a study of 298 children with a history of penicillin allergy, only 1 (0.3%) had a positive FEIA result for penicillin.[21] In another study, 132 patients referred to an allergy specialty group were tested by FEIA and 3% were positive.[22] Our center found that even among patients with a diagnosis of "penicillin, amoxicillin, or cephalosporins allergy" based on a contemporaneous examination by a physician and the label "allergic" being placed in the medical record, only 34% were found to have an IgE reaction determined by skin testing or oral challenge.[23] Thus, physician-diagnosed allergic reactions to BLAs based on patient examination at the time of the

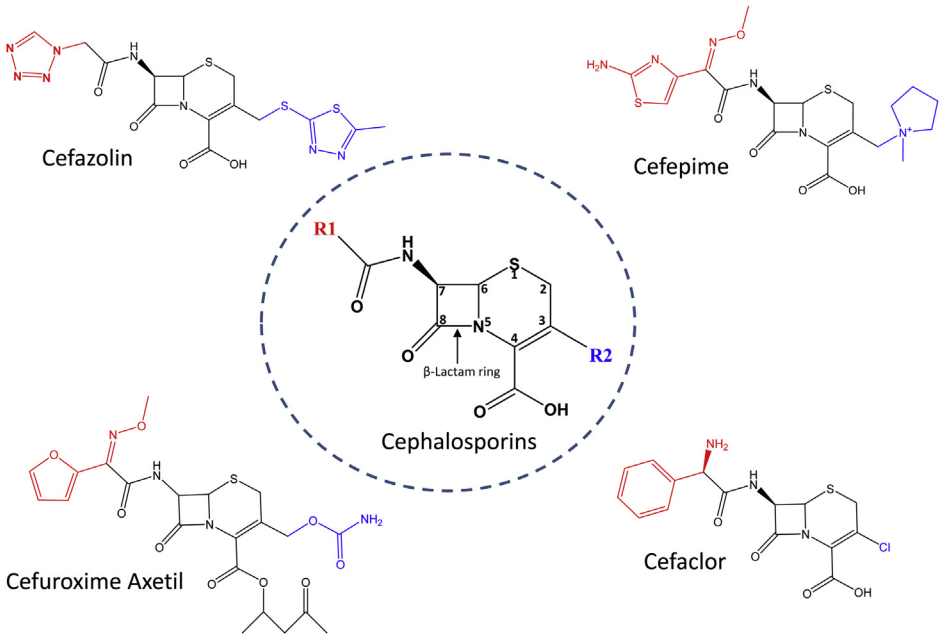


Figure 2. Basic structure of cephalosporins. Core structure of cephalosporin along with selected drugs showing the diversity of the R1 and R2 side chains.

reaction is more accurate than patient history alone, but even so there is considerable overdiagnosis.

Second, penicillin allergy is not due to reactions to the β-lactam ring. For many years the allergenic sensitivity to penicillin was thought to be due to the β-lactam ring, with minor allergic reactivity attributed to the R group. If that were true, then cross-sensitivity among all penicillins should be observed, which is certainly not correct. The penicillin β-lactam ring opens during metabolism in the body, but it does not fragment like the cephalosporin β-lactam ring.[24,25] Parts of the β-lactam rings of both penicillins and cephalosporins are likely cleaved along with side chain structures to form potential antigenic compounds. Benzylpenicillin, where the R group is a benzyl compound, is commonly known as penicillin G, a naturally occurring penicillin (vs different penicillin compounds made synthetically) and is the criterion standard for testing. Early work suggested that the β-lactam ring of penicillin was highly reactive and could spontaneously form the penicilloyl structure under physiologic conditions. Presumably, this inherent instability is what plagued Dr Fleming's early attempts at trying to maintain its activity. Moreover, in vitro studies led to the notion that the β-lactam opened in vivo by the action of an attack of a free amine group, presumably on a protein in the plasma or a cell membrane, resulting in the covalent attachment of the penicilloyl to a protein carrier (Fig 3).[26] The resulting structure of the attached penicillin G is a benzylpenicilloyl. For skin testing, benzylpenicilloyl is attached to polylysine and commercially supplied as penicilloyl polylysine (Pre-Pen; AllerQuest LLC, Plainville, Connecticut).[27] Penicilloyl polylysine is often called the major antigenic determinant of penicillin. In vitro studies also led to the notion that penicillin G could also be metabolized in vivo to other products, such as its alkaline hydrolysis product benzylpenicilloate, its acid hydrolysis product benzylpenilloate, and benzylpenicilloyl-*n*-propylamine. These molecules, including penicillin G, became termed *minor antigenic determinants* and are called a *minor determinant mixture* (MDM) and increase the accuracy of skin testing with penicilloyl polylysine.[17,19,20,24,28–34]

Similar to penicillins, a cephalosporin determinant, cephalosporyl, is derived from nucleophilic disruption of the β-lactam ring by the amino group of plasma or cell membrane proteins.[35] However, the resulting compound, unlike benzylpenicilloyl, is unstable and undergoes a process of multiple fragmentations of the dihydrothiazine ring.[36] Although there is more fragmentation of the cephalosporyl grouping, the side chain structure usually remains intact and is the major factor for cross-reactivity between cephalosporins and penicillins.[37,38]

Early evidence supporting that allergy to penicillins is not directed to the β-lactam ring came from studies of patients allergic to penicillins. Some patients who had an immediate reaction to amoxicillin had tolerance to penicillin G or other penicillins.[39–41] These authors conclude that the allergy reactions are directed toward the side chain of amoxicillin. However, this does not rule out the involvement of the penicillin β-lactam-thiazolidine backbone in either the native penicillin or minor determinant product as being a component of the antigenic determinant. In a study investigating the reactivity of penicillin G–induced human T-cell clones to various penicillin derivatives, proliferation of one clone was dependent on both the side-chain and the penicillin β-lactam-thiazolidine backbone, whereas no proliferation was observed using just the penicillin β-lactam-thiazolidine backbone.[42] These data suggest that the antigenic determinant structure/conformation may involve both the side chain and the penicillin β-lactam-thiazolidine backbone.

Third, the predictive value of penicillin skin testing may be enhanced using MDM. The value of including the MDM in an appropriate panel of reagents for skin testing was proven in the National Institute of Allergy and Infectious Disease (NIAID) clinical trial of skin testing with penicillin determinants. In the NIAID study, 99% of patients with negative skin test results to penicillin that include the MDM can safely receive penicillin, even those with a history of penicillin reaction.[17] In a separate study, skin testing with only penicilloyl polylysine and penicillin identified 84.2% of patients with a positive result using a more complete reagent panel that included amoxicillin, penicilloate, and penilloate.[43]

Fourth, cephalosporin allergy does not occur in approximately 10% of penicillin allergic patients. Articles published in the late 1960s and early 1970s reported cross-reactivity rates of 8% to 18%. This became an established teaching and appeared in the package insert of early cephalosporins even though no studies were performed; the misperception was that patients with a history of a penicillin allergy would be at a 10% risk of an adverse reaction if given a cephalosporin.[11,44]

Cross-reactivity between penicillins and cephalosporins mainly stems from whether their R1 side chains are structurally similar

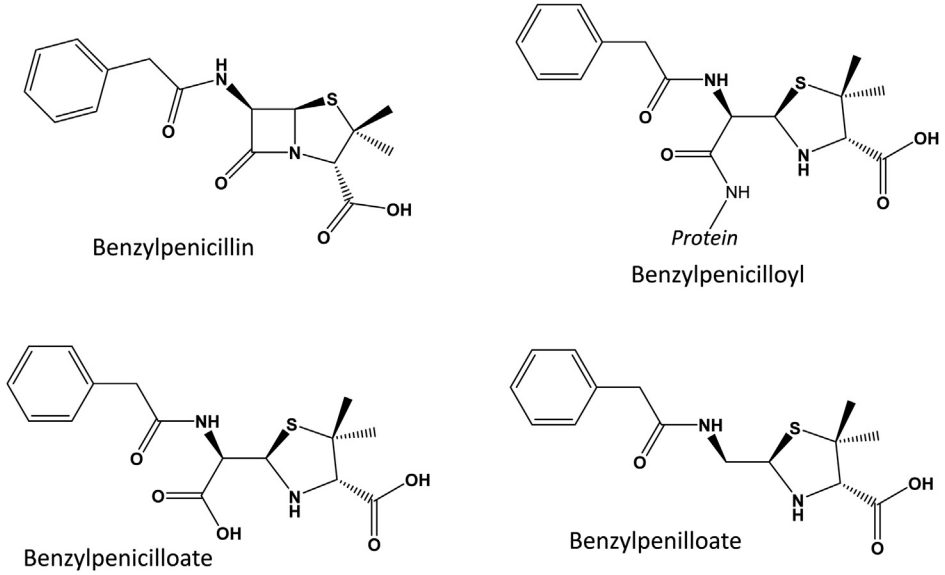


Figure 3. Metabolized benzylpenicillin products. Benzylpenicilloyl is the major determinant shown covalently attached to a protein, whereas benzylpenicilloate and benzylpenilloate are minor determinants.

and not due to similarity in the β-lactam rings (Table 2). A meta-analysis of all articles published from 1960 to 2005 found 9 source articles as an evidence base.[7] A significant increase in allergic reactions to cephalothin (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.1-5.5), cephaloridine (OR, 8.7; 95% CI, 5.9-12.8), and cephalexin (OR, 5.8; 95% CI, 3.6-9.2), and all first-generation cephalosporins plus cefamandole (OR, 4.8; 95% CI, 3.7-6.2) were observed in penicillin allergic patients; no increase was observed with second-generation cephalosporins (OR, 1.1; 95% CI, 0.6-2.1) or third-generation cephalosporins (OR, 0.5; 95% CI, 0.2-1.1). From the results, it was concluded, "First-generation cephalosporins have cross-allergy with penicillins, but cross-allergy is negligible with second and third-generation cephalosporins. Particular emphasis should be placed on the role of chemical structure in determining the risk of cross-reactivity between specific agents."[7] In a subsequent review of 644 penicillin allergic children, the cross-reactivity to a cephalosporin depended on the generation of the cephalosporin (also strongly correlated with differences in the R1 side chain) that varied from 23.9% to 0.3%, with the first- and second-generation showing the highest and the third generation the lowest.[45] Another review found the overall cross-reactivity between penicillins and cephalosporins in individuals who report a penicillin allergy to be approximately 1% and, in those with a confirmed penicillin allergy, 2.55%.[11] However, not all structurally related side chains will have cross-reactivity to penicillins because compounds with dissimilar structures yet similar biosostere properties (similar 3-dimensional electronic and steric properties) might result in cross-reactivity as observed between the benzyl group of penicillin G and the thiophene side chain of cephalothin.[37,46,47] Although plausible, it has also been suggested that the cross-reactivity between penicillin G and cephalothin may be the common methylene group within the side chains.[47,48] Within this same study, a weak determinant of cross-reactivity between cephalothin and cefoxitin was speculated to encompass the β-lactam ring.[48] Evidence that the β-lactam ring is not the major antigenic determinant comes from trials of patients with positive penicillin skin test results and subsequent testing for sensitivity to a carbapenem, which only shares the common β-lactam ring structure.[49–52] The authors conclude that there is a low rate of cross-reactivity (0.8%-1%) between penicillins and carbapenems. In other cases where patients have positive skin test results to both penicillins and cephalosporins, it is not clear if there is true cross-reactivity or natural coreactivity to these drugs.[53] In conclusion, the major allergic cross-reactivity between penicillins and cephalosporins is directed toward the side chains. This finding has allowed safe treatment of penicillin allergic patients with various cephalosporin drugs.

Fifth, cephalosporin allergy does not cross all generations of the antibiotic class. Cross-reactivity among cephalosporins stems from whether their R1 and/or R2 side chains are structurally similar and not the β-lactam rings. Patients have been described with IgE reactivity to penicillin and cephalosporins where the side chains of both drugs are dissimilar.[53] However, in that study, coexisting but separate allergen sensitivities to a cephalosporin and penicillin may have occurred because of prior exposures. Table 3 lists structurally similar R1 side chain groups and possible cross-reactivity within the group due to the similar R1 structures. The cephalosporin ring does not maintain its native structure in vivo; it breaks into several pieces[54-56] while preserving the R1 and R2 side chains that act to interfere with penicillin-binding proteins structural integrity.

Table 2
Structural similarities of cephalosporins to penicillin derivatives[a]

100% Identical R1 side chain	Similar R1 structural components
Cefaclor [Second] (Ampicillin)	Cefamandole [Second]
Cefadroxil [First] (Amoxicillin)	Cefonicid [Second]
Cefatrizine [First] (Amoxicillin)	
Cefprozil [Second] (Amoxicillin)	
Cephalexin [First] (Ampicillin)	
Cephaloglycin [First] (Ampicillin)	
Loracarbef [Second] (Ampicillin)	

[a]The generation of the cephalosporin drug is shown in brackets. Penicillin derivative whose R side chain is 100% identical to the cephalosporin R1 side chain is shown in parentheses. These drugs are either known to elicit an allergic reaction in penicillin allergic patients or, due to their similarity to the penicillin derivative, suggested to be avoided in patients with known allergies to those penicillins (Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics*. 2005;115:1048-1057; Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients: a literature review. *J Emerg Med*. 2012;42:612-620; Pichichero ME. Evidence supporting the use of cephalosporin antibiotics in penicillin-allergic patients. *Pediatr Asthma Allergy Immunol*. 2005;18:230-246; Dickson SD, Salazar KC. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. *Clin Rev Allergy Immunol*. 2013;45:131-142).

Skin Testing and FEIA

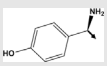
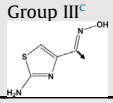
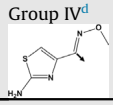
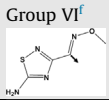
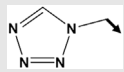
Most patients receiving penicillins or cephalosporins will produce specific IgG and IgM antibodies without experiencing any adverse reaction,[57] so their detection in patients has no clinical correlation. The 1992 NIAID study previously cited found that more than 98% of patients with a history of penicillin allergy but who were skin test negative could safely receive the antibiotic.[17] The NIAID study and others established that skin testing with the correct panel of reagents can be highly accurate.[17,30,58,59] There is a low incident rate (0%-3%) of patients with a negative penicillin skin test result and who had a previous history of penicillin allergy may sometime in the future develope an allergy to penicillin, known as resensitization.[60,61]

Other methods may be used to test for IgE antibodies to penicillin, such as FEIA or the enzyme-linked immunosorbent assay (ELISA). FEIA testing is more likely to detect clinically irrelevant IgE to penicillins and cephalosporins than skin testing and is not as reliable as skin testing.[24,30] There is inadequate evidence to rely on those methods with the same anticipated accuracy of skin testing.

Cephalosporin Skin Testing

Penicillin skin testing does not reliably predict cephalosporin allergy because cephalosporin allergy is driven by the side chain structure and not the similarity in β-lactam ring structure. In vitro studies have proven that IgE antibodies reacting with cephalosporins can identify a range of antigenic determinants, including a portion of a side chain to a full side chain, the side chain and part of the β-lactam ring, or the whole cephalosporin compound.[47,48,62–64]

Table 3
Cephalosporin drugs with similar R1 side-chain structures

Group I[a]	Group II[b]	Group III[c]	Group IV[d]	Group V[e]	Group VI[f]	Group VII[g]	Group VIII
							
Identical Cefaclor Cephaloglycin Loracarbef Cephalexin Similar Cefamandole Cefonicid	Identical Cefadroxil Cefatrizine Cefprozil	Identical Cefdaloxime Cefdinir	Identical Cefepime Cefteram Ceftiolene Cefditoren Cefetamet Cefmenoxime Cefodizime Cefoselis Cefotaxime Cefpirome Cefpodoxime Ceftizoxime Ceftriaxone Cefquinome Similar Cefixime Ceftazidime Less similar Ceftibuten Cefcapene	Identical Cephaloridine Cephalothin Cefoxitin	Identical Cefozopran Cefclidine Similar Ceftobiprole Cefluprenam Less similar Ceftaroline fosamil	Identical Cefazolin Ceftezole	Dissimilar Cefazedone Cefbuperazone Cefmetazole Cefminox Cefotetan Cefoperazone Cefpiramide Cefsulodin Cefuroxime Cephacetrile Cephapirin Cephradine Flomoxef Moxalactam

[a]This grouping contains a benzylmethanamine core except for cefamandole and cefonicid, which contains a core of benzylmethanol.
[b]This grouping contains a 4-(aminomethyl)phenol core.
[c]This grouping contains a (*E*)-2-aminothiazole-4-carbaldehyde oxime core.
[d]This grouping contains a (*E*)-2-aminothiazole-4-carbaldehyde *O*-methyl oxime core except for cefixime, which contains an attached formic acid to *O*-methyl oxime; ceftazidime, which contains an attached propionic acid to *O*-ethyl oxime; ceftibuten, which contains a *but*-3-enoic acid moiety in place of the formaldehyde *O*-methyl oxime moiety; and cefcapene, which contains a but-1-en-1-yl moiety in place of the formaldehyde *O*-methyl oxime group.
[e]This grouping contains a 2-methylthiophene core, except for cefoxitin, which also contains a 7-methoxy group on the β-lactam ring.
[f]This grouping contains a (*E*)-5-amino-1,2,4-thiadiazole-3-carbaldehyde *O*-methyl oxime core except for ceftobiprole, which contains *O*-methyl oxime replaced with oxime; cefluprenam, which contains *O*-methyl oxime replaced with *O*-fluoromethyl oxime; and ceftaroline fosamil, which contains the (*E*)-5-amino- group replaced with a (E)-5-phosphonoamino- group and the *O*-methyl oxime replaced with a *O*-ethyl oxime group.
[g]This grouping contains a 1-methyl-1*H*-tetrazole core.

Skin testing reveals cross-reactivity in some patients between penicillins and first-generation cephalosporins that share side chain identity, namely, between ampicillin-amoxicillin and cephalexin-cefadroxil. This is not the case with second-, third-, or fourth -generation cephalosporins that have distinct side chains from those of penicillin-amoxicillin.[6,45,65,66] Skin testing for cephalosporins has been undertaken in more than 20 studies, but the positive and negative predictive values of the results are less well established. Currently, cephalosporin skin tests are performed with the native molecule and can only predict hypersensitivity to the cephalosporin skin test reagent or cephalosporins with similar side chains. Cephalosporin minor determinant mixtures could be prepared in the same manner as penicillin MDM, but to date no such reagents have been prepared and tested in a study population.

Attributable Risk

Three major factors should be considered in attributing a causal association between penicillin allergy and cephalosporin allergy. First, the term *allergic* was used in many reports without definition, and careful reading of those articles allows a conclusion that nonallergic reactions were included in the calculation of risk.[67] Second, the 2 largest case series in the early literature[44,68] involved nearly exclusively first-generation cephalosporins in an era when their production was likely due to the contamination with penicillin. The early overestimation of cross-reactivity was the contamination of the early cephalosporin antibiotics with trace amounts of penicillin as noted above.[11,69,70] Third, there is a 3-fold increased coincidental risk of adverse reactions to unrelated drugs among penicillin-allergic patients.[15] The occurrence of an allergic reaction to a cephalosporin in a penicillin-allergic patient does not prove causality because it may be completely coincidental. Specifically, if there is an independent risk for a cephalosporin allergy of 2% and such a patient receives penicillin and is later given a cephalosporin, then the patient may have a reaction to the cephalosporin that has nothing to do with cross-reaction to penicillin.

Skin Testing Reagents

Approximately 95% of the penicillin bound to tissue proteins is in the penicilloyl (major determinant) form.[26,71] Therefore, prior work suggested testing with penicillin G and benzyl-penicilloyl polylysine reagent, which detects approximately 93% of penicillin allergic patients.[72] However, our work and others support testing with both major and minor determinants.[17,19,20,24,32,33] Both the American Joint Task Force on Practice Parameters and the European Network for Drug Allergy guidelines for skin testing include MDM along with penicilloyl polylysine and other possible β-lactam drugs for initial skin testing.[34,38,73,74] Currently, there is no commercial MDM preparation available for purchase in the United States. The preparation of the MDM reagent is not difficult in a laboratory because it is well described as involving acid base chemical treatments of penicillin G.[32,75] The problem with commercial manufacture is that MDM preparations must be used promptly or stored frozen at −80°C, where the preparation remains stable for prolonged intervals. The pharmaceutical industry has been asked to supply penicilloyl polylysine and the MDMs penilloate and penicilloate for testing worldwide.[76] Studies have begun to challenge

the need for using MDM probably in light of the difficulty in obtaining MDM reagents. In a recent report, Macy and Ngor[31] evaluated 500 patients with a proven history of penicillin allergy with a skin test using only penicilloyl polylysine, penicillin, and amoxicillin and, if the results were negative, followed by oral amoxicillin challenge. Eight patients had a positive IgE-mediated penicillin reaction, 4 to the skin test and 4 to the oral challenge. The 4 who were missed by the skin test but reacted to the oral challenge presented a mild treatable rash. By not skin testing with the minor determinants penilloate and penicilloate, the authors admit that they may have missed approximately 10% of potential patients in the initial skin testing, but these patients would have been identified in the oral challenge. Because none of the patients were found to be positive for amoxicillin in this cohort, this Southern California Permanente Medical Group, which provides all physician services for Kaiser Permanente in Southern California, has stopped using amoxicillin as a skin test reagent. However, in other countries where amoxicillin drug treatment is high, addition of amoxicillin to the skin test is required for diagnosis.[29,38]

The semisynthetic penicillins amoxicillin and ampicillin contain an amine group in their side chain and are therefore called aminopenicillins. These aminopenicillins both have an identical benzyl penicillin side chain, but amoxicillin contains an additional hydroxyl group at the *para*-C4 position on the benzyl ring. Early studies included ampicillin in a skin test panel for suspected penicillin allergic patients.[39,77–79] In light of the studies mentioned above, the question of whether skin testing with ampicillin is required has been raised.

Skin testing to cephalosporins is limited to use of the native drug and to those agents available as parenteral preparations. Currently, no studies have identified minor determinants of cephalosporins and validated testing has not been established. The allergist is left to identify the best match between the suspected culprit cephalosporin and the closest match to a parenteral drug as possible, based on side-chain structure. Fortunately, the most commonly used cephalosporins in hospital are parenteral drugs, which makes skin testing feasible. The most common cephalosporins used in community-based practices are ceftriaxone (a parenteral agent) and oral cephalosporins. Therefore, an allergist may be able to substitute parenteral compounds that contain similar R side-chain groups to the oral drug for skin testing (eg, cefuroxime parenteral and cefuroxime axetil oral).

Elective Penicillin and Cephalosporin Allergy Evaluation

Mendelson et al[80] described a method of routine elective penicillin allergy skin testing. One of the authors (M.E.P.) extended this approach to include penicillin, ampicillin, and cephalosporin elective allergy skin testing.[23] In this way, the urgent consultation can be avoided, and nearly all patients tested can be cleared for subsequent use of the suspected drug with considerable cost savings to the patient and health care system. The method is well described.[23,80] In brief, elective allergy evaluation allows the avoidance of antihistamines that may interfere with skin test interpretation. The skin test reagent panel can be broad to include penicillin G, penicilloyl polylysine, MDM, ampicillin, and a panel of cephalosporin reagents to represent the class and drugs likely to be needed in the future (eg, cefazolin, cefuroxime, and ceftriaxone). If the skin test result is negative, then it is necessary to proceed to an open oral challenge. The skin testing confirms the absence of circulating and sensitized memory B cells but does not rule out the possibility of a dormant allergy (especially if the reaction was several months to years earlier) with quiescent memory B cells to the antibiotic allergen. An open oral challenge can be undertaken because no detectable circulating sensitized memory B cells are present. The open oral challenge is typically performed for 5 days with a selected antibiotic, then a 3-day washout, and then a 5-day oral challenge with a second antibiotic. At worst a gradual buildup of sensitized cells may produce a pruritic rash or urticaria. The oral challenge can also allow identification of non-Coombs and Gell classification reactions. After the oral challenge, the patient is recalled for repeat testing to identify subclinical activation of allergy sensitization. The approach should allow a determination and confirmation of bona-fide hypersensitivity or the absence thereof for a group of β-lactams and permit the allergist to provide the patient and primary care physician with advice on which antibiotics in the class must be avoided and which can be taken. Of course, subsequent sensitization can occur, but that risk is the same as any patient.

Cross-Allergy Among Other β-Lactams

Carbapenems

Prospective studies of carbapenems suggest that attributable cross-reactivity is very unlikely or absent between these β-lactams and penicillins-cephalosporins.[49,50]

Monobactams

Monobactams do not have cross-allergy with penicillins and most cephalosporins.[74] An exception is aztreonam because there is both immunologic and clinical data that support a cross-reaction with ceftazidime because both drugs share an identical side chain.[81]

β-Lactamase Inhibitors

One of the mechanisms that has evolved in the resistance to BLAs is the bacterial incorporation of a gene that encodes a β-lactamase enzyme that attacks the labile β-lactam ring. There are β-lactamase inhibitors that are themselves β-lactams, such as clavulanic acid, and although these alone are poor antibiotics, in combination with a BLA, they may overcome the bacterial resistance. One such combination drug contains amoxicillin and clavulanic acid (Augmentin).[9] In one study group of 276 patients who experienced an allergic reaction after administration of amoxicillin–clavulanic acid, 30% of immediate allergic reactions were selective reactions to clavulanic acid.[82]

Risk of Anaphylaxis

The incidence of anaphylaxis to penicillins, calculated from a comprehensive international survey, is 0.015% to 0.004%, with a fatality rate of 0.002% to 0.0015%.[16] More limited data suggest the rate of anaphylaxis from cephalosporins is 0.1% to 0.0001%.[69] A summary of cases of anaphylaxis induced by cephalosporins was recently summarized.[3] There are more reported cases of anaphylaxis to cephalosporins in patients without a known penicillin allergy compared with those with known penicillin allergy.[67,83]

Conclusion

This evidence-based review teaches that the incidence of allergic reactions to penicillins is much lower than widely thought. Penicillin skin testing and FEIA is used for type I immune testing. Neither skin testing nor FEIA testing is of any value in detecting risk of type II to IV reactions. The classic approach for predictive penicillin allergy has been the skin test using penicilloyl polylysine and MDMs. If an ampicillin or amoxicillin allergy is suspected, then one may include ampicillin or amoxicillin to predict ampicillin-amoxicillin allergy. Currently, penicillin skin testing using only penicilloyl polylysine and penicillin followed by an oral challenge with amoxicillin is now considered to be adequate in evaluating a type I penicillin allergy.[31] Allergy to penicillins (and cephalosporins) is caused mainly by reactions to the side chains of the molecules and less commonly to the

β-lactam ring. Cephalosporin allergy in penicillin allergic patients is attributable to cross-reactive antibodies to side-chain similarity of the cephalosporin to penicillin or amoxicillin. Cephalosporin allergy may result from cross-reactivity among cephalosporin compounds if the R1 or R2 side chains of the cephalosporins are identical or similar. Anaphylaxis from cephalosporins is rare. There is no evidence of an increased risk of anaphylaxis to cephalosporins in penicillin-allergic patients. Likewise, there is little risk of allergy to carbapenems, monobactams, and β-lactamase inhibitors that lack identical or similar side chains to penicillin in penicillin allergic patients.

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